Osteoporos Int (2010) 21:1237–1245
DOI 10.1007/s00198-009-1064-1

ORIGINAL ARTICLE

Independent from muscle power and balance performance, a creatinine clearance below 65 ml/min is a significant and independent risk factor for falls and fall-related fractures in elderly men and women diagnosed with osteoporosis

L. Dukas · E. Schacht · M. Runge

Received: 28 December 2008 / Accepted: 26 August 2009 / Published online: 22 September 2009

Abstract
Summary We assessed in a cross-sectional study in elderly men and women with osteoporosis, the association between the creatinine clearance (CrCl) and the performance in different balance and muscle power and function tests and found that a decreasing creatinine clearance was significantly associated with lower balance and muscle power.
Introduction To determine if a creatinine clearance of <65 ml/min is significantly associated with decreasing muscle power and balance and an increased risk for falls and fractures.
Methods We assessed in a cross-sectional-study in 1781 German osteoporotic patients, the association between the CrCl, the physical performance, and the number of falls and fractures.
Results Controlling for age, gender, BMI, and osteoporosis treatment (fracture analysis only), a decreasing CrCl was associated with lower physical performance in the timed-up-and-go test (corr −0.2337, $P<0.0001$), chair-rising test (corr −0.1706, $P<0.001$), and tandem-stand test (corr 0.2193, $P<0.0001$), and a CrCl of <65 ml/min was associated with a significantly higher risk for falls (47.7% vs. 36.2%, $P=0.0008$) and fall-related fractures (33.1% vs. 22.9%, $P=0.0003$) compared with a CrCl of ≥65 ml/min.
Conclusions In this study, we found a significant gender-independent correlation between decreasing CrCl and lower performance in balance and muscle power tests. Reduced muscle power and balance may therefore be involved in the low creatinine clearance associated increased risk for falls and fall-related fractures. Furthermore, we found that a CrCl <65 ml/min., independent from the performance in muscle power, muscle function, and balance tests, is a significant risk factor for falls and fractures.

Keywords Balance · Creatinine clearance · Falls and fractures · Muscle power

L. Dukas
Department of Medicine, Acute Geriatric University Clinic, Basel, Switzerland

L. Dukas (✉)
Ambulatorium Wiesendamm,
Wiesendamm 22,
4057 Basel, Switzerland
e-mail: l.d@gmx.net

E. Schacht
Zürich Osteoporosis Research Group ZORG,
Zollikerberg, Switzerland

M. Runge
Aerpah Clinic Esslingen,
Esslingen, Germany

Introduction

The predisposition of older individuals to falls, which often results in mobility difficulties and functional decline, is due to the accumulation of impairments and comorbid conditions with aging, such as muscle weakness, decreased balance, neuromuscular abnormalities, concomitant arthritis, and chronic diseases [1].

In addition to its vital role in bone formation and remodeling and maintenance of bone mass, D-hormone (calcitriol) has been shown to be important for the maintenance of muscle strength, muscle power, and function and balance in older individuals [2–4]. Three

randomized controlled trials [5–7] reported a significant reduction in the frequency of falls with calcidiol in institutionalized elderly women with vitamin deficiency [5] or with either calcitriol [6] or alfacalcidol [7] in community-dwelling, vitamin D replete elderly women and men [25(OH) D>30 ng/ml, as defined by the WHO]. In a 4-year observational study, Faulkner et al. described a significant association between higher calcitriol serum levels and a reduced risk for falls [8]. These observations may be explained by the effect of D-hormone on muscle power and function as well as on balance. Through a highly selective D-hormone receptor, D-hormone acts directly on muscle tissue [9] by mediating de novo protein synthesis and affecting muscle cell growth and differentiation of muscle fibers [10, 11].

Recent published studies found a significant association between the creatinine clearance, decreasing serum levels of calcitriol, and an increased risk for falls and osteoporotic fractures [7, 8, 12–16]. The objective of this study was to test the hypothesis that a low creatinine clearance below 65 ml/min, as a surrogate for decreasing calcitriol serum levels, is associated with lower performance in muscle power and balance tests, number of falls and fallers, and fall-associated fractures in older community-dwelling independent persons diagnosed with osteoporosis.

Subjects and methods

This is a cross-sectional German study conducted from May 2005 till October 2005, with the aim to assess the association between the creatinine clearance and the performance in different muscle power and balance tests, the number of falls and fallers, and fall-associated fractures in osteoporotic German women and men aged 65 years and older.

Two hundred eighty-seven medical centers from all over Germany participated in this study. GP's, specialists in internal medicine, and orthopedists, who are involved in the treatment of osteoporotic patients, were asked to fill in a questionnaire concerning their patients treated for osteoporosis and to perform different muscle power and balance tests. The questionnaire had to be filled out in the presence of and with the help of the patient treated for osteoporosis at a medical visit during the study time period. The three muscle tests are from the official German guidelines for the assessment of the patient's risk for falls.

The questionnaire gave information on some demographic parameters (gender, age, weight, height), the date of diagnosis of osteoporosis (DD/MM/YY), method of diagnosis [dual energy X-ray absorptiometry (DEXA), ultrasound, X-rays], duration of osteoporotic treatment (options: from-till, respectively; long term therapy), and type of antiosteoporotic treatment (options: bisphosphonates, fluorides, calcitonins, raloxifen, others, no therapy, known vertebral deformations (yes/no), number of falls within the last 12 months (intrinsic nonsyncopal/syncopal), number of osteoporotic fractures within the last 12 months, circumstances and numbers of fractures (in association with falls, no association with falls, numbers), localization of fall-related fractures, localization of nonfall-related fractures, and serum creatinine level and creatinine clearance (calculated). The questionnaire gave no information on how and with which method the fractures were diagnosed. The creatinine clearance was calculated using the well-established formula from Cockcroft-Gault adjusted for gender [17]. Compared with a direct measurement of the glomerular filtration rate (GFR) with 24-h urine sampling or inuline clearance, the Cockcroft-Gault formula gives only an estimate of the GFR. Nevertheless, the Cockcroft-Gault formula is widely accepted and used as an easy tool for the calculation of the creatinine clearance. Participants treated with alfacalcidol or calcitriol were excluded from the study.

Falls were defined as “unintentionally coming to rest on the ground, floor, or other lower level”. The study physicians received training in the use of the fall protocol (date, time, circumstances, and injuries).

The diagnostic criteria for osteoporosis used by the physician were not assessed. Therefore, in this study, the diagnosis of osteoporosis is solely based on the physicians report. Falls were defined as being either intrinsic nonsyncopal falls or syncopal falls. However, a more precise classification of the intrinsic nonsyncopal falls was not performed. Fracture incidence within the last 12 months was assessed as documented in the medical history of each individual participant and not on patients recall.

Functional assessment

The association between the creatinine clearance and functional mobility and balance measured with the timed-up-and-go (TUG) test, the tandem standing test (TST), and the chair rising test (CRT) was the main outcome of the analyses of this cross-sectional study. The study physicians and their nurses received training in the performance of these tests.

The TUG test reported by Podsialdo and Richardson is a measure of functional mobility and tests muscle function, gait speed, and balance [18]. The TUG test is an effective method of assessing functional mobility efforts needed in everyday life [18]. The concept is appealing because it describes a realistic mobility assessment including potential fall situations, such as transfer in and out of a chair, walking, and turning [19]. The person is observed and

timed while arising from an arm chair (seat height 48 cm; arm height 68 cm), walking 3 m at a normal speed, and going around an obstacle on the floor (i.e., a brick at 3-m distance from the chair), returning, and sitting down again. Subjects are allowed to use the arms of the chair to get up. Only one trial has to be performed. The longer a patient needs to perform the TUG the lower his performance. Recently, it has been shown in a 10-year longitudinal study that the TUG is not only a measurement of functional mobility but that it can also be used as a predictor for nonvertebral fractures: a 1-SD (2.6 s) increase in TUG performance was, in this study, associated with a 24% increase in the risk for nonvertebral fractures [20].

The TST, as described by Guralnik et al. and Gill et al. [21, 22], tests balance capacity. The individual is asked to stand in a position with feet held tight and close for 10 s, then to stand at a semitandem for 10 s, and then at a full tandem where both feet are directly in line, the heel of the leading foot directly in front of the toes of the other. A maximum of three attempts is allowed from which the best performance is being counted. Inability to stand in this position for at least 10 s indicates a high risk for falls. The longer a patient can hold his position in the TST the better his performance.

In the chair rising test, for testing muscle power [19, 21, 23], an individual is asked to stand up and sit down five times from a chair of usual height as quickly as possible without using the arms. The arms are crossed in front of the chest. Only one trial has to be performed. An individual who is not able to sit and rise five times or performs the test in more than 10 s is at high risk to fall. The longer a patient needs to perform the CRT the lower his performance.

Statistical analysis

For the main analyses, we used Spearman's correlation analyses, logistic regression analyses, and pooled linear regression models to control simultaneously for several potentially confounding variables. Comparisons of means were performed by multivariate adjusted analyses of variance [24]. Since age and body mass index (BMI) distributions were markedly skewed, logarithmic transformation of these variables were performed prior to analyses. Since TUG was not normally distributed, we used log transformed TUG. We included covariates used in the models which we suggested or were suggested in previous studies [25, 26] to be associated with functional performance. These covariates were gender (male, female), which was analyzed as a dichotomous variable; age; BMI; and creatinine clearance, which were analyzed as continuous variables. For all other analyses, we used *t* test, Wilcoxon rank-sum test, and Chi-square test.

For all analyses, we used SAS version 9.1 by the SAS Institute Inc., Cary, NC, USA, licensed to the University of Basel, Switzerland.

Data, Safety, and Monitoring Board, established by GWD Consult Germany (Safety and Monitoring Board: GWD Consult, Research Contract, Postfach 1210, 63152 Mülheim/Main, Germany), reviewed the conduct of the study.

Results

Demographics (Table 1)

One thousand four hundred ten (79.2%) women and 371 (20.8%) men participated in this study (Table 1). The mean age of the study participants was 74.2 years, and participants were slightly overweight with a mean body mass index of 26.1 kg/m^2.

Women in this study group were slightly older than men [mean age, 74.6 years (age range, 61–99 years) vs. mean age 72.9 years (age range, 61–90 years)]. Concerning the performance in the muscle and balance tests, women were significantly slower than men in the chair rising test (mean performance time, 13.5 vs. 12.1 s, $p=0.05$), whereas for the TUG and the TST, there was no statistical significance difference between genders (Table 1).

Creatinine clearance, osteoporosis, osteoporotic treatment, and falls

Participants in this study had a mean creatinine clearance of 60.2 ml/min 1,130 (63.5%) participants had a CrCl of <65 ml/min. Women were significantly more prone to have a low creatinine clearance than men (68.65% vs. 43.67%, $p<0.0001$).

In the 1,410 participants, osteoporosis was diagnosed in 19.9% of the participants within the study year, and for the majority of the 1,410 participants (63.75%), osteoporosis was known for not more than 5 years. Only a minority of 16.35% had a long-time diagnosis of osteoporosis of more than 5 years. Osteoporosis was diagnosed in 42.7% by DEXA only, in 17.4% with DEXA and X-ray (total DEXA 60.1%), in 4.4% with ultrasound of the calcaneus, and in 34.5% with X-ray only. At the time of the study, 36.4% of the 1,410 participants received a treatment with bisphosphonates, 4.6% with fluorides, 3.8% with calcitonin, 2.2% with raloxifen, and 3.8% received other not specified therapy for osteoporosis. Of the 1,410 participants, 54.2% received no specific therapy for osteoporosis, and for 9.4% of the 1410 participants, there was no information on treatment. Of all 1,410 patients, 61.2% were under a treatment with vitamin D and calcium.

Table 1 Characteristics of subjects and physical performance in muscle and balance tests according to gender and according to a creatinine clearance of <65 ml/min vs. ≥65 ml/min

	Gender		*p* Value	Gender				*p* Value[a]*
	Men	Women		Men		Women		
CrCl (ml/min)				<65	≥65	<65	≥65	
Age (years)	74.6	72.9	≤0.0001	75.2	71.2	76.0	71.4	<0.001
BMI (kg/m²)	26.4	26.0	0.074	25.6	27.0	25.1	27.9	<0.001
TUG (s)	12.4	11.8	0.11°	13.1	10.7	12.9	11.3	0.042[a]
TST (s)	9.9	10.0	0.85°	9.1	10.6	9.6	10.6	0.004[a]
CRT (s)	13.5	12.1	0.005°	13.1	11.0	14.1	12.0	0.012[a]
Falls[b] (%)	43.1	43.8	0.26[a]	47.5	39.7	47.7	35.1	0.01
Fall-associated fractures (%)	35.9	36.0	0.66[a]	45.1	28.7	40.1	26.9	<0.001

CrCl creatinine clearance in milliliters per minute, *BMI* body mass index in weight (kilograms) per height (squaremeter), *TUG* timed-up-and-go test, *TST* tandem stand test, *CRT* chair rising test

[a] Controlled for age, BMI, and the use of vitamin D and calcium (and for the fracture analyses, type of osteoporosis treatment)

[b] Falls during study time in percent of the population

[*] *p* Value for the difference between CrCl <65 ml/min vs. ≥65 ml/min

Of the participants, 70.4% presented vertebral deformations, which were significantly present in more participants with a creatinine clearance of <65 ml/min than in participants with a creatinine clearance of ≥65 ml/min (73.4% vs. 64.3%, $p<.0001$).

Within the last 12 months before the study visit, a total of 907 falls were registered. From the participants who reported a fall, 43.1% reported a single fall and 56.9%, multiple falls. Participants with a creatinine clearance of less than 65 ml/min reported significantly more non-syncopal falls and were prone to experience multiple falls than participants with a creatinine clearance of ≥65 ml/min (47.7% vs. 36.2%, $p = 0.0008$, multivariate controlled and 28.0% vs. 18.4%, $p<0.001$, multivariate controlled, respectively). For syncopal falls, we found no significant difference between groups according to the creatinine clearance (<65 ml/min vs. >65 ml/min; 9.7% vs. 13.8%, $p=0.13$). Treatment of osteoporosis did not affect falls.

Performance in the different muscle power and balance tests, the creatinine clearance, and the association to fall incidence (Table 1 and Fig. 1)

A CrCl of ≤65 ml/min was controlled for age, gender, and BMI, compared with a CrCl of ≥65 ml/min, and associated with a significantly higher incidence for falls (OR, 1.40; 95% CI 1.12–1.74, $p=0.002$) and a significantly higher risk for multiple falls (OR, 1.42; 95% CI 1.09–1.85, $p=0.010$). A decreasing CrCl was controlled for age, gender, and BMI significantly associated with lower performance in the TUG test (corr −0.2337, $p<0.0001$), in the chair rising test (corr −0.1706, $p<0.0001$), and the tandem stand (corr 0.2193, $p<0.0001$). These findings were significant in both genders. However, the correlation coefficient for all tests was higher in men.

Accrodingly, to this finding, participants with a creatinine clearance of <65 ml/min had controlled for age, gender, and BMI, significant lower performance in the TUG (13.0 vs. 11.1 s, $p=0.005$), the TST (9.5 vs. 10.6 s, $p<0.001$), and CRT (14.0 vs. 11.7 s, $p=0.003$) compared with participants with a creatinine clearance of ≥65 ml/min.

The timed-up-and-go test as well as the TST were significantly associated with the number of falls (point

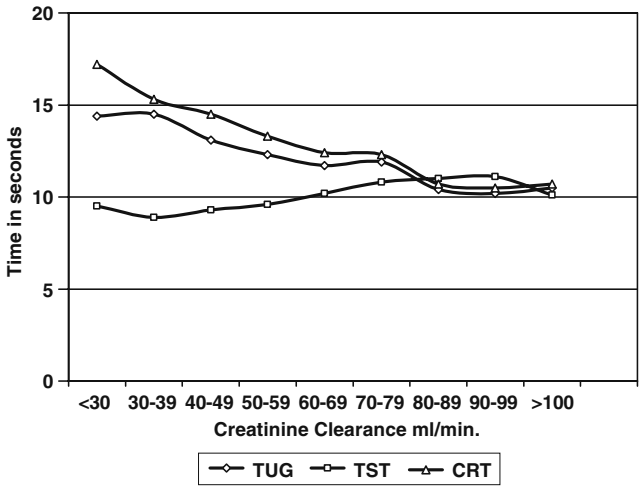

Fig. 1 Physical performance in different muscle power and balance tests, TUG (*open diamond*), TST (*open square*), and CRT (*open triangle*), according to the creatinine clearance

estimate, −0.05, $p<0.0007$; res., 0.06, $p<0.0001$) and the number of frequent fallers (point estimate, −0.05, $p<0.0002$; res., 0.07, $p<0.0001$), whereas the CRT was not associated to the incidence of falls ($p=0.43$) but to the number of frequent fallers (point estimate, 0.028, $p=0.02$). Multivariate controlled, including for the performances in the TUG, TST, and CRT a low CrCl of <65 ml/min, still remained a significant predictor for falls (OR, 1.35, 95%CI 1.06–1.73, $p=0.016$) and for the number of frequent fallers (OR, 1.40, 95% CI 1.04–1.87, $p=0.023$).

Fall-associated fractures and creatinine clearance (Fig. 2)

Of the participants, 36% experienced a fall-related fracture within the last 12 months ($N=641$) including 6.7% who experienced more than one fall-related fracture. Patients with a creatinine clearance of <65 ml/min experienced significantly 44% more fall-related fractures than participants with a creatinine clearance of ≥65 ml/min (33.1% vs. 22.9%, $p=0003$, multivariate controlled). In 95%, the localization of the fracture was specified—39.5%vertebral fractures, 20.4% hip fractures, 26.3% fractures of the radius, and 13.8% other localization (mostly of the feet and shoulder/humerus). Participants with a creatinine clearance of <65 ml/min had controlled for age, gender, BMI, and osteoporosis treatment, significantly more vertebral fractures (OR, 1.50, 95% CI 1.04–2.15, $p=0.03$), hip fractures (OR, 1.82, 95% CI 1.14–2.91, $p=0.012$), and fractures of the radius (OR, 1.73, 95% CI 1.15–2.60, $p=0.012$) but not significantly more fractures of other localization (OR, 1.54, 95% CI 0.68–3.51, $p=0.205$) than participants with a creatinine clearance of ≥65 ml/min.

The incidence of fall-associated fractures was significantly associated to the creatinine clearance ($p<0.0001$). We observed a stepwise increase of fall-associated fractures: participants with a creatinine clearance of ≥70 ml/min had a mean risk of 28.9% to experience a fall-associated fracture. With a creatinine clearance between <70 ml/min and ≥40 ml/min, participants had a mean 45.3% to experience a fall-associated fracture or a significant 1.56 increased risk compared with participants with a creatinine of ≥70 ml/min ($p<0.001$). Below 40 ml/min, this risk increased to a mean risk of 71.6% to experience a fracture while falling or a 2.47 increased risk compared with participants with a creatinine of ≥70 ml/min ($p<0.0001$).

A total of 137 nonfall-associated fractures were registered, mostly vertebral fractures ($N=113$, 82.5%). We found no significant statistical difference for nonfall-associated fractures according to the creatinine clearance (<65 ml/min vs. ≥65 ml/min, 7.9% vs. 6.9%, $p=0.46$).

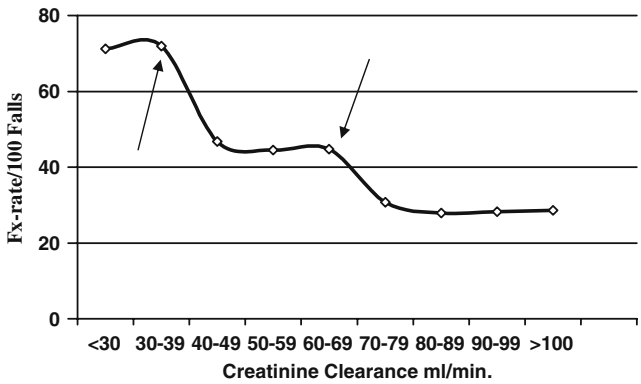

Fig. 2 Fracture rate per 100 falls according to the creatinine clearance

Discussion

In this study, we observed that osteoporotic elderly men and women with a low creatinine clearance of <65 ml/min showed significantly poorer performance in muscle and balance tests, experienced significantly more falls and fractures, and were significantly more prone to be frequent fallers than osteoporotic elderly men and women with a creatinine clearance of ≥65 ml/min. A low creatinine clearance of <65 ml/min, as a surrogate marker for decreasing calcitriol serum levels, was independent from the performance in muscle power and balance tests significantly associated with a higher incidence of falls and fractures.

A reduction in demands for health care resources in older individuals can be achieved by maintaining functional capacity and mobility in order to keep older persons independent [27–29]. Ways of improving and maintaining function with aging is an important research and public health agenda. There is improving evidence that alfacalcidol and calcitriol, besides their well-known effects on bone metabolism [30, 31], enhance muscle power [32, 33] and reduce falls and fall-associated fractures in older persons [6, 7, 14, 15]. Muscle weakness affects balance and functional mobility, which puts an older person at increased risk of falling and fractures [34]. The association between calcidiol, D-hormone, and muscle strength has been investigated in preclinical studies, observational studies, and randomized controlled trials, and the majority of these studies are consistent with the proposition that activated vitamin D is important, if not essential, for normal muscle strength [11]. In previous reports, it was shown that ambulatory older men and women with higher D-hormone serum concentrations had better leg extension power [2] and better muscle function [4] compared with older persons with low D-hormone serum concentrations. Stein and colleagues observed low calcidiol and high parathormone (PTH) serum concentrations in elderly fallers [35]. Faulkner et al. showed that only higher D-hormone concentrations are

significantly associated with a lower risk of falls in older community-dwelling women, whereas vitamin D supplementation and calcidiol and PTH concentrations were not associated with either neuromuscular function or falls [8].

Aging is associated with impaired renal function [36, 37] easily measurable as deterioration of the creatinine clearance, which leads to decreased activity of the renal 1α-hydroxylase [38–40] and, consecutively, to low D-hormone serum levels [41–43]. Muscle strength, balance, and functional mobility depend on D-hormone serum levels [2, 4, 6, 10, 37, 44–47]. In a recently published case-control study including almost 700 women aged 65 years or older, Ensrud et al. showed that the risk of new hip fracture increases 2.3 times in women with moderate impairment of renal function (CrCl of <45 ml/min) and 1.6 times in women with a CrCl of 45 to 59 ml/min compared with women with a CrCl >60 ml/min [16]. The risk for trochanteric hip fracture was even higher and increased 7.2-fold in women with a CrCl of <45 ml/min and 3.9-fold in those with a CrCl of 45 to 59 ml/min compared with women with a CrCl of >60 ml/min [16]. However, the risk of vertebral fractures was not significantly associated with renal function [16]. These results are in line with a cross-sectional and a prospective longitudinal study including 1,713 healthy community-dwelling men and women with an average age of 71 years [37]. The Rancho Bernardo study found a significant linear association between renal function and hip bone mineral density. In addition, a significant association has been shown between renal function and tandem gait and speed of gait [37]. It was shown in several studies [6, 7] that a treatment with D-hormone (alfacalcidol and calcitriol, respectively) significantly reduced the risk of falls and of fall-associated fractures. One study showed that treatment with alfacalcidol in community-dwelling elderly men and women with a low CrCl of <65 ml/min significantly decreases the low CrCl-associated high risk for falls [13]. In another placebo controlled study with 489 women aged 65–77 years, Gallagher et al. confirmed recently that a low CrCl of <60 ml/min is a statistically significant predictor of falls [15], and in his study, he found a similar risk for falls and fall-related fractures as we reported in this study [15]. A similar risk for falls and fall-related injuries was also described in the study by Gryfe et al. [48]. In the low CrCl group (<60 ml/min) in the Gallagher et al. study [15], the rate of falls decreased with a 3-year D-hormone treatment by 53% ($p=0.003$) and by 30% in the group with a CrCl of >60 ml/min. In the placebo group, women with a CrCl <60 ml/min had at baseline 60% higher rate of history of falls compared with the group with CrCl ≥60 ml/min ($p=0.007$). Compared with women with a CrCl of ≥60 ml/min, women with a CrCl of <60 ml/min had, in addition, lower calcium absorption ($p<0.001$), lower serum D-hormone ($p<0.001$), lower physical performance, and normal serum 25 (OH)D ($p<0.05$) suggesting that there is a decreased conversion of 25(OH)D to 1,25(OH)2D (D-hormone) when the CrCl decreases below 60 ml/min. Besides the lower kidney mass in the elderly, increased CRP, higher cytokine serum levels, and/or elevated concentrations of fibroblast growth factor 23, which is produced to maintain normal phosphatemia, inhibit renal 1α-hydroxylase activity, and some of these factors may also have a direct detrimental effect on bone quality and muscle power [40, 49, 50]. In summary, a low creatinine clearance is associated with an increased risk for osteopenia and osteoporosis [14, 15, 27, 37, 51], lower physical performance, increased falls and hip fractures, and possibly, increased frailty. Our results and the results from other studies [2, 4, 6, 11, 15, 16, 20, 34–36, 38, 50, 52] allow us to theorize that calcitriol is directly involved in the causal pathogenic pathway of decreased muscle strength, decreased balance and related falls and fractures, and that a decreasing calcitriol serum level and/or a low concentration at the target organs is a risk factor for falls and fall-related fractures. However, in this study, we showed, indirectly (using a creatinine clearance of <65 ml/min as a surrogate for decreasing calcitriol serum levels), that, independent from muscle strength and balance performance, a decreasing calcitriol serum level is a risk factor for falls and fall-related fractures. Therefore, we conclude that, calcitriol, besides its influence on muscle and bone, may have other effects, i.e., on neuromuscular transmission and cognition. Few studies exist on this subject. The brain has calcitriol receptors [53], and it has been shown that calcidiol as well as calcitriol [54] serum levels are significantly correlated to cognitive function and the performance in different cognitive test and depression in older adults, respectively [55]. In animal studies, it was shown that Vitamin D Receptor (VDR) receptor knockout mice have muscular and motor impairments that significantly affect locomotor behavior [11, 56].

It is postulated that an increase in D-hormone in serum and/or at the target organs would up-regulate VDR in muscles although one cannot exclude an up-regulation of VDR in brain and an effect on the central nervous system [15, 57].

Interestingly, instead of a continuous increase of the risk of fall-associated fractures, we observed in this study a stepwise increase, namely, a 56% increased risk with a CrCl between 40 and 70 ml/min and a 147% increased risk with a CrCl of <40 ml/min compared with a CrCl of ≥70 ml/min. As described previously, we and others observed a significant decline of D-hormone serum levels with a CrCl of <65 ml/min. A CrCl-dependent increase of intact parathormone (iPTH) serum levels was described by different authors [38, 58, 59] when the CrCl decreases below 40 ml/min. We therefore raise the hypothesis that the risk of fall-associated fractures increases in two steps: first,

when it comes to a critical CrCl-associated cut point of decreasing D-hormone serum levels and a second increase in the risk of fall-associated fractures, when it comes to a critical CrCl-associated increase in iPTH serum levels. Further studies are needed to confirm our findings. If confirmed, this would open new and tremendous possibilities of a much more differentiated approach of the treatment of fall-associated fractures.

Our study has several limitations. The results are from a cross-sectional study with its well-known limitations of interpretation. The outcome variable "falls" was assessed by recall with the inherent recall bias. Concerning the fall-associated fractures, we also did not assess how the fractures were diagnosed or confirmed, and we did not assess history of fractures, which would have been an important control variable for this outcome variable. In general, we also could not control for other important covariates such as comorbid conditions, number of medications, physical activity, and other not-assessed control variables. Therefore, we cannot rule out uncontrolled confounding. Furthermore, the diagnosis of osteoporosis was solely based on different radiological methods. We can therefore not rule out a miss-classification concerning the diagnosis of osteoporosis. We can assume that this possible miss-classification concerns the whole study group and does not influence our result on the influence of a low creatinine clearance on the muscle power and balance performance as well as on frequency of falls and fractures in this population. The participants were Caucasian elderly men and women over the age of 65 years treated for osteoporosis. The diagnosis of osteoporosis was not for all participants based on BMD. Therefore, our findings are not generalizable to a general osteoporotic population, to a younger population, or to osteoporotic men and women of other races.

In summary, we found that muscle power and balance performance, as assessed by the TUG, TST, and CRT tests, are significantly related to the creatinine clearance. A creatinine clearance of <65 ml/min is associated with poorer performance in all muscle and balance tests. Surprisingly, a low CrCl of <65 ml/min was independent from the performance in muscle power and balance tests significantly associated with a higher incidence of falls and fall-related fractures. Since a low creatinine clearance of <65 ml/min can be considered as a surrogate marker for low calcitriol serum levels, we conclude therefore that preventive health and rehabilitation strategies should aim to correct D-hormone deficiency in elderly men and women with a creatinine clearance of <65 ml/min in order to maintain muscle power and balance and to prevent falls and fall-associated fractures.

Low CrCl seemed to be a prognostic tool for low hip BMD, low bone strength, decreased muscle performance, increased risk of falls and fall-related fractures, and possibly, of frailty. A very useful diagnosis of the frailty syndrome defined by decreased bone strength, decreased mobility, decreased cognitive capabilities, and increased risk of falls and fractures, especially hip fractures, may be a simple calculation of CrCl from serum creatinine based on the Cockcroft-Gault formula. This attractive hypothesis must be confirmed in further clinical studies because it would be of great economic relevance to delay the frailty before it transfers to disability.

Acknowledgement We are indebted to Manfred Klasser, auditor and GWD consult, for his precise and meticulous monitoring.

Conflicts of interest This study was supported by TEVA Pharmaceuticals Industries Ltd., Israel.

References

1. Tinetti ME, Inouye SK, Gill TM et al (1995) Shared risk factors for falls, incontinence, and functional dependence. Unifying the approach to geriatric syndromes. JAMA 273(17):1348–1353
2. Bischoff HA, Stähelin HB, Urscheler N et al (1999) Muscle strength in the elderly: its relation to vitamin D metabolites. Arch Phys Med Rehabil 80(1):54–58
3. Pfeifer M, Begerow B, Minne HW et al (2000) Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. J Bone Miner Res 15(6):1113–1118
4. Dukas L, Staehelin HB, Schacht E, Bischoff HA (2005) Better functional mobility in community-dwelling elderly is related to D-hormone serum levels and a to a daily calcium intake. Nutr Health Aging 9(5):347–351
5. Bischoff HA, Stähelin HB, Dick W et al (2003) Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial. J Bone Miner Res 18:343–351
6. Gallagher JC (2004) The effects of calcitriol on falls and fractures and physical performance tests. J Steroid Biochem Mol Biol 89–90:497–501
7. Dukas L, Bischoff HA, Lindpaintner LS, Schacht E, Birkner-Binder D, Damm T, Thalmann B, Stähelin HB (2004) Alfacalcidol reduces the number of fallers in a community-dwelling elderly population with a minimum calcium intake of 500 mg daily. J Am Geriatr Soc 52:1–7
8. Faulkner KA, Cauley JA, Zmuda JM, Landsittel DP, Newman AB, Studenski SA, Redfern MS, Ensrud KE, Fink HA, Lane NE, Nevitt MC (2006) Higher 1,25-dihydroxyvitamin D3 concentrations associated with lower fall rates in older community-dwelling women. Osteoporos Int 17(9):1318–1328
9. Boland R (1986) Role of vitamin D in skeletal muscle function. Endocr Rev 7:434–447
10. Sorensen OH, Lund BI, Saltin B et al (1979) Myopathy in bone loss of aging: improvement by treatment with 1 alpha-hydroxycholecalciferol and calcium. Clin Sci 56(2):157–161
11. Endo I, Inoue D, Mitsui T, Umaki Y, Akaike M, Yoshizawa T, Kato S, Matsumoto T (2003) Deletion of vitamin D receptor gene in mice results in abnormal skeletal muscle development with deregulated expression of myoregulatory transcription factors. Endocrinology 144(12):5138–5144
12. Dukas L, Schacht E, Stahelin HB (2005) In elderly men and women treated for osteoporosis a low creatinine clearance of

<65 ml/min is a risk factor for falls and fractures. Osteoporos Int 16(12):1683–1690
13. Dukas LC, Schacht E, Mazor Z, Stahelin HB (2005) A new significant and independent risk factor for falls in elderly men and women: a low creatinine clearance of less than 65 ml/min. Osteoporos Int 16(3):332–338
14. Dukas L, Schacht E, Mazor Z, Stahelin HB (2005) Treatment with alfacalcidol in elderly people significantly decreases the high risk of falls associated with a low creatinine clearance of <65 ml/min. Osteoporos Int 16(2):198–203
15. Gallagher JC, Rapuri PB, Smith LM (2007) An age related decrease in creatinine clearance is associated with an increase in number of falls in untreated women but not in women receiving calcitriol. J Clin Endocrinol Metab 92:51–58
16. Ensrud KE, Lui L-Y, Taylor BC, Ishani A, Shlipak MG, Stone KL, Cauley JA, Jamal SA, Antoniucci DM, Cummings SR, for the Study of Osteoporotic Fractures Research Group (2007) Renal function and risk of hip and vertebral fractures in older women. Arch Intern Med 167:133–139
17. Cockcroft DW, Gault MH (1976) Prediction of creatinine clearance from serum creatinine. Nephron 16(1):31–41
18. Podsialdo D, Richardson S (1991) The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc 39(2):142–148
19. Mathias S, Nayak US, Isaacs B (1986) Balance in elderly patients: the "get-up and go" test. Arch Phys Med Rehabil 67(6):387–389
20. Zhu K, Devine A, Prince RL (2008) Timed Up and Go Test and BMD as predictors of fractures: a 10-year longitudinal study. J Bone Min Res 23:s119
21. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB (1995) Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. N Eng J Med 332:556–561
22. Gill TM, Williams CS, Tinetti ME (1995) Assessing risk for the onset of functional dependence among older adults: the role of physical performance. J Am Geriatr Soc 43:603–609
23. Runge M, Rehfeld G, Resnicek E (2000) Balance training and exercise in geriatric patients. J Musculoskel Neuronal Interact 1:54–58
24. Winer BJ (1971) Statistical principles in experimental design, 2nd edn. McGraw Hill, New York, p 514
25. Skeleton DA, Greig CA, Davies JM (1994) Strength, power and related functional ability of healthy people aged 65–89 years. Age Ageing 23:371–377
26. Danneskiold-Samsøe B, Kofod V, Munter J (1984) Muscle strength and functional capacity in 78–81 year old men and women. Eur J Appl Physiol 52:310–314
27. McMurdo ME (1997) Physical activity and health in old age. Scott Med J 42(5):154–155
28. Rejeski WJ, Mihalko SL (2001) Physical activity and quality of life in older adults. J Gerontol A Biol Sci Med Sci 56:23–35 Spec No 2(2)
29. Lee MS, Tanaka K (1997) Significance of health fitness appraisal in an aging society. Appl Human Sci 16(4):123–131
30. Schacht E (1999) Rationale for treatment of involutional osteoporosis in women and for prevention and treatment of corticosteroid-induced osteoporosis with alfacalcidol. Calcif Tissue Int 65:317–327
31. Lau KHW, Baylink DJ (1999) Vitamin D therapy of osteoporosis: plain vitamin D therapy versus active vitamin D analog (D-hormone) therapy. Calcif Tissue Int 65:295–306
32. Richy F, Deroisy R, Lecart M-P, Hanssens L, Mawet A, Reginster J-Y (2005) D-hormone analog alfacalcidol: an update on its role in post-menopausal osteoporosis and rheumatoid arthritis management. Aging Clin Exp Res 17:133–142
33. Schacht E, Richy F, Reginster J-Y (2005) The therapeutic effects of alfacalcidol on bone strength, muscle metabolism and prevention of falls and fractures. J Musculoskelet Neuronal Interact 5:273–284
34. Tinetti ME, Williams CS (1998) The effect of falls and fall injuries on functioning in community-dwelling older persons. J Gerontol A Biol Sci Med Sci 53(2):M112–M119
35. Stein MS, Wark JD, Scherer SC, Walton SL, Chick P, Di Carlantonio M, Zajac JD, Flicker L (1999) Falls related to vitamin D and parathyroid hormone in Australian nursing home and hostel. J Am Ger Soc 47:1195–1201
36. Klawansky S, Komaroff E, Cavanaugh PF, Mitchell DY, Gordon MJ, Connelly JE, Ross SD (2003) The relationship between age, renal function and bone mineral density in the US population. Osteoporos Int 14:570–576
37. Jassal SK, von Muhlen D, Barrett-Connor E (2007) Measures of renal function, BMD, bone loss, and osteoporotic fracture in older adults: the Rancho Bernardo study. J Bone Miner Res 22:203–210
38. Trombetti A, Stoermann-Chopard C, Ferrari S, Saudan P, Chevalley T, Binet I, Uebelhart B, Rizzoli R, Martin PY (2003) Prävention von Knochenkomplikationen bei Patienten mit chronischer Niereninsuffizienz (1.Teil). Swiss Med Forum 11:260–266
39. Slovik DM, Adams JS, Neer RM et al (1981) Deficient production of 1,25-dihydroxyvitamin D in elderly osteoporotic patients. N Engl J Med 305:372–374
40. Oelzner P, Muller A, Deschner F, Huller M, Abendroth K, Hein G et al (1998) Relationship between disease activity and serum levels of vitamin D metabolites and PTH in rheumatoid arthritis. Calcif Tissue Int 62:193–198
41. Epstein S, Bryce G, Hinman JW et al (1986) The influence of age on bone mineral regulating hormones. Bone 7:421–425
42. Tsai KS, Heath H III, Kumar R et al (1984) Impaired vitamin D metabolism with aging in women: possible role in pathogenesis of senile osteoporosis. J Clin Invest 73:1668–1672
43. Dukas L, Bischoff HA, Schacht E et al (2002) Normal 25 (OH) vitamin D serum levels do not exclude D-hormone deficiency in community-dwelling elderly. Osteoporos Int 13(1): S35
44. Peacock M, Heyburn P (1977) Effect of vitamin D3 metabolites on proximal muscle weakness. Calcif Tiss Res 24(Suppl):R20–R23
45. Verhaar HJJ, Samson MM, Jansen PAF et al (2000) Muscle strength, functional mobility and vitamin D in older women. Aging Clin Exp Res 12:455–460
46. Dhesi JK, Bearne LM, Monitz C, Hurley MV, Jackson SHD, Swift CG, Allain TJ (2002) Neuromuscular and psychomotor function in elderly subjects who fall and the relationship with vitamin D status. J Bone Miner Res 17:891–897
47. Koike T, Okawa T, Wada M, Kita T, Takaoka K (2003) Effects of a long-term alfacalcidol or calcitonin administration on body sway in Japanese elderly women. J Bone Miner Res 18(S2)):S168
48. Gryfe CI, Amies A, Ashley MJ (1997) A longitudinal study of falls in an elderly population: incidence and morbidity. Age Aeing 6(4):201–210
49. Liu S, Tang W, Zhou J et al (2006) Fibroblast growth factor 23 is a counter-regulatory phosphaturic hormone for vitamin D. J Am Soc Nephrol 17:1305–1315
50. Cappola AR, Xue QL, Ferrucci L, Guralnik JM, Volpato S, Fried LP (2003) Insulin-like growth factor I and interleukin-6 contribute synergistically to disability and mortality in older women. J Clin Endocrinol Metab 88:2019–2025
51. K/DOQI Practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 2003;42(4, S3):S7-S28
52. Zofkovà I, Kancheva RL, Bendlovà B (1997) Effect of 1,25(OH)2 vitamin D3 on circulating insulin-like growth factor-I and β2

microglobulin in patients with osteoporosis. Calcif Tissue Int 60:236–239
53. Jorde R, Waterloo K, Saleh F, Haug E, Svartberg J (2006) Neuropsychological function in relation to serum parathyroid hormone and serum 25-hydroxyvitamin D levels. The Tromso study. J Neurol 253(4):464–470
54. Miya K, Morimoto S, Fukuo K, Imanaka S, Shiraishi T, Yamamato H, Kitano S, Miyashita Y, Inoue T (1991) Hirotani J. Nippon Ronen Igakkai Zasshi 28(1):34–39
55. Przybelski RJ, Binkley NC (2007) Is vitamin D important for preserving cognition? A positive correlation of serum 25-hydroxyvitamin D concentration with cognitive function. Arch Biochem Biophys 460(2):202–205
56. Burne TH, McGrath JJ, Eyles DW, Mackay-Sim A (2005) Behavioural characterization of vitamin D receptor knockout mice. Behav Brain Res 157(2):299–308
57. Wiese RJ, Uhland-Smith A, Ross TK, Prahl JM, DeLuca HF (1992) Up-regulation of the vitamin D receptor in response to 1,25-dihydroxyvitamin D3 results from ligand-induced stabilization. J Biol Chem 267:20082–20086
58. Francis RM, Peacock M, Barkworth SA (1984) Renal impairment and its effects on calcium metabolism in elderly women. Age Ageing 13:14–20
59. Nguyen TV, Eisman JA, Kelly PJ, Sambrook PN (1996) Risk factors for osteoporotic fractures in elderly men. Am J Epidemiol 144:255–263